an animal or human. The therapeutic agent may be administered orally, topically or via injection by itself, or additionally may be provided as a pharmaceutical composition comprising the therapeutic agent and a biologically acceptable carrier. The inventive compositions can be, but are not limited to aqueous solutions, emulsions, creams, ointments, suspensions, gels, and liposomal suspensions. Particularly preferred biologically acceptable carriers include but are not limited to water, saline, Ringer's solution, dextrose solution and solutions of ethanol, glucose, sucrose, dextran, mannose, mannitol, sorbitol, polyethylene glycol (PEG), phosphate, acetate, gelatin, collagen, Carbopol, and vegetable oils. It is also possible to include suitable preservatives, stabilizers, antioxidants, antimicrobials, and buffering agents, for example including but not limited to BHA, BHT, citric acid, ascorbic acid, and tetracycline. The therapeutic agents of the presently claimed invention may also be incorporated or encapsulated in a suitable polymer matrix or membrane, thus providing a sustained-release delivery device suitable for implantation near the site to be treated locally.

In the Claims:

Please cancel claim 4, amend claims 1-3 as indicated in attached Appendix B ("Version With Markings to Show Changes Made") and add new claims 5-21. Copies of the amended claims, in the form they will take after entrance of this Amendment, are presented below. A clean copy of *all* of the claims that will be pending in the case after entrance of the present Amendment is provided in the attached Appendix C ("Clean Copy of All Claims Pending After Entrance of the Present Amendment"):

1. (Amended) A method for the combinatorial biosynthesis of one or more compounds comprising:

a) providing one or more starter units, wherein said one or more starter units have incorporated therein a functional handle that reacts with a functionality present on a solid support unit, the starter units being accepted as substrates for one or more modular

biosynthetic enzymatic machinery systems;

b) attaching said one or more starter units to a solid support unit to provide one or more support bound starter units;

c) providing said one or more support bound starter units to said one or more biosynthetic enzymatic machinery systems to generate a collection of template structures;

d) functionalizing said template structures using synthetic organic chemistry; and

e) repeating steps c) and/or d) until a desired support bound collection of structures is generated.

2. (Amended) The method of claim 1 further comprising functionalizing said support bound collection of structures generated in step e) to provide a support bound collection of unnatural natural products.

3. (Amended) A method for the combinatorial biosynthesis of one or more compounds comprising:

a) providing one or more starter units, wherein said one or more starter units have incorporated therein a functional handle that reacts with a functionality present on a solid support unit, the starter units being accepted as substrates for one or more modular biosynthetic enzymatic machinery systems;

b) attaching said one or more starter units to a solid support unit to provide one or more support bound starter units;

c) providing said one or more support bound starter units to said one or more biosynthetic enzymatic machinery systems to generate a collection of template structures; and

d) functionalizing said collection of structures to provide a support bound collection of unnatural natural products.

4. Cancelled

5. The method of claim 1 further comprising the step of cleaving said support bound collection of structures from said solid support unit.

6. The method of claim 2 or 3 further comprising the step of cleaving said support bound collection of unnatural natural products from said solid support unit.

7. The method of claim 1, 2 or 3 wherein the functional handle is a chemically robust functionality, which includes an alkyne, an olefin or an iodoalkene.

8. The method of claim 1, 2 or 3 wherein the step of attaching the starter units to the solid support unit is effected by a chemical reaction which includes Glaser coupling, olefin metathesis or Stille coupling reaction.

9. The method of claim 1, 2 or 3 wherein the biosynthetic enzymatic machinery systems comprise one or more naturally-occurring synthetic enzymes.

10. The method of claim 9 wherein the biosynthetic enzymatic machinery systems comprise one or more enzymes which include fatty acid synthase, polyketide synthase, peptide synthase or terpene (or isoprenoid) synthase.

11. The method of claim 1, 2 or 3 wherein the biosynthetic enzymatic machinery systems comprise one or more modified enzymes.

12. The method of claim 11 wherein the modified enzyme is a genetically modified enzyme.

13. The method of claim 11 wherein the modified enzyme is a class I polyketide synthase enzyme.

14. The method of claim 1, 2 or 3 wherein the structure of one or more starter units incorporates an antibody recognition element.

15. The method of claim 1, 2 or 3 wherein one or more template structures incorporate an antibody recognition element.

16. The method of claim 1, 2 or 3 wherein the step of functionalizing said template structures is carried out using combinatorial techniques including, but not limited to, parallel synthesis and split-and-pool synthesis.

17. The method of claim 1, 2 or 3 wherein the step of functionalizing the template structures includes attaching a biomolecule to said template structures.

18. The method of claim 17 wherein the biomolecule includes polysaccharides, nucleic acids, peptides, and polymers.

19. The method of claim 1, 2 or 3 further comprising the step of recording the reaction history using an encoding technique.

20. The method of claim 19 wherein the encoding technique is selected from the group consisting of spatial encoding techniques, graphical encoding techniques, chemical encoding techniques and spectrometric encoding techniques.

21. The method of claim 20 wherein the spectrometric encoding technique is selected from the group consisting of mass spectroscopy, fluorescence emission and nuclear magnetic resonance spectroscopy.

REMARKS

Claims 1-4 are currently pending in the subject application. Claims 1-3 have been amended, claim 4 has been cancelled and claims 5-21 have been newly added. Applicants respectfully submit that no new matter is added with these amendments or additions. Applicants additionally reserve the right to re-introduce the subject matter of cancelled claim 4 in continuing or divisional applications.

Amendment of Specification

The specification has been amended in order to more clearly set forth what is intended as Applicants' invention, or to correct a typographical or clerical error. Applicants respectfully submit that no new matter is added with these amendments.

Amendment of Claims

The claims have been amended in order to more clearly set forth what is intended as Applicants' invention, to expedite prosecution or to correct a typographical or clerical error, and are not amended for the purpose of distinguishing prior art. Specifically, claims 1-3 have been amended to more clearly state that the starter units are substrates of the enzymatic systems and to recite that the collection of structures generated in practicing the invention is support bound. Support for this amendment can be found throughout the specification, specifically on page 3 lines 6-14 and page 7 lines 20-22. Applicants submit that these amendments do not present new matter.

Addition of Claims

Claims 5-21 have been added and Applicants submit that these additions do not present new matter. Specifically, support for newly added claims 5-6 can be found on pages 10-12 where it is recited that in certain embodiments the starter units are bound to a solid support unit using "split and pool" and parallel synthesis techniques. A person of ordinary skill in the art will recognize that such solid phase synthetic techniques typically involve a linker to attach the substrate molecule to the solid phase. As synthesis proceeds, this material is transformed to product with desired functionalities, which product can be finally removed by cleavage of the linker. An important

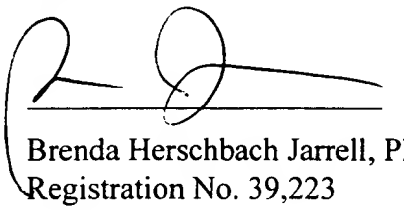
requirement is that the linker be a chemically robust moiety (*i.e.*, one which is not altered when exposed to the various chemical conditions used in the course of the synthesis) so that it may be cleaved to release the final compounds from the solid support. Additional support for newly added claims 5 and 6 can be found on page 9 lines 16-29 where it is recited that the starter units or template structures may be bound to a solid support via a functionality that will not interfere with, or be altered by, the chemistry being employed, which functionality comprises a *cleavable* bond (see line 17).

Additionally, Claims 7 and 8 have been added to recite examples of functional handles that can be used in certain embodiments of the present invention, as well as exemplary reactions to immobilize the starter units on the solid support. Support for such addition can be found on page 8 lines 17-19 and page 9 lines 16-29. Claims 9-13 have been added to recite elements pertaining to the biosynthetic enzymatic machinery systems described in the present invention, specifically that the biosynthetic enzymatic machinery systems comprise naturally-occurring enzymes or modified enzymes (support for which addition can be found in the paragraph entitled "Biosynthetic Enzymatic Machinery" from page 5 line 25 through page 6 line 28). Claim 12 recites elements pertaining to genetically modified enzymes, which claim finds support in Figure 4 and on page 10 lines 8-16. Additionally, support for claims 14 and 15 can be found on page 5 lines 12-14 where it is recited that in certain embodiments specific functionalities can also be incorporated in to the template structures via the original starter unit capable of being recognized by an antibody. Claim 16 finds support on pages 10-12 where it is recited that in certain embodiments the starter units are bound to a solid support unit using "split and pool" and parallel synthesis techniques. Support for claims 17-18 can be found on page 14 lines 28-30. Finally claims 19-21 have been added to recite elements pertaining to encoding techniques for recording the reaction history (support for which addition can be found on page 12 lines 24-32 and page 13 lines 5-26).

Applicants submit that the amendments to the claims and specification, as described above and detailed herein, do not present new matter. Thus Applicants respectfully request entry of these amendments, and consideration of these amendments in processing the application.

Please charge any fees that may be associated with this matter, or credit any overpayments, to our Deposit Account No. 03-1721.

Respectfully submitted,



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